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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,875	03/27/2001	Eric B. Kmiec	Napro-4	2466

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EXAMINER
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ANGELL, JON E

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 05/23/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/818,875	KMIEC ET AL.
	Examiner	Art Unit
	J. Eric Angell	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 29 April 2002.

2a) This action is FINAL.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 25-77 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 25-77 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_\_

**DETAILED ACTION**

Claims 25-77 are pending in the application.

***Election/Restrictions***

1. Applicant's election without traverse of Group II in Paper No. 11 is acknowledged.  
Election of the species SEQ ID No. 358 without traverse in Paper No. 11 is also acknowledged.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
3. Claims 25-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25 and 75 are drawn to a method of targeted sequence alteration of a nucleic acid comprising: combining the targeted nucleic acid in the presence of cellular proteins with a single stranded oligonucleotide 17-121 nucleotides in length, said oligonucleotide having an internally unduplicated domain of at least 8 contiguous deoxyribonucleotides (emphasis added).

However, the originally filed application does not disclose oligonucleotides having an internally unduplicated domain of at least 8 contiguous deoxyribonucleotides. In the amendment

filed March 7, 2002, Applicants assert that support for an internally unduplexed domain of at least 8 contiguous nucleotides is found, for example, on page 7, line 20. It is noted that page 7, line 20 reads, "The central DNA domain is generally at least 8 nucleotides in length." There is no disclosure that can be found anywhere in the specification that the oligonucleotide comprises an internally unduplexed domain of at least 8 deoxyribonucleotides. Furthermore, it is not apparent in the figures that any of the oligonucleotides comprise an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides. Therefore, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 26-74, 76 and 77 are dependent claims and are rejected for the same reasons.

4. Claims 25-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for targeted sequence alteration of a nucleic acid using oligonucleotides, and encompass altering genetic material for the treatment of disease. Therefore the nature of the invention is a method of gene therapy; specifically, therapeutic gene targeting.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass gene targeting of any gene, in any cell type, in any species including prokaryotes, and all eukaryotes, including humans. The claims also encompass gene targeting in cells *in vitro*, *ex vivo* and *in vivo*. Furthermore, the claims encompass producing any type of genetic alteration, such as base substitution, and addition/deletion of any number of bases.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as efficient modes of delivering therapeutic nucleic acid to target cells had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches that all of the human gene therapy studies have been plagued by inconsistent results, and sites specific examples (see page 409, first col.). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still

no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects).

Regarding therapeutic gene targeting, Yanez et al. (Gene Therapy; Vol. 5, p. 149-159; 1998) teaches, "While gene targeting has been achieved both in human cell lines and in non-transformed primary human cells, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by *in vivo* gene targeting is therefore impractical without dramatic improvements in targeting efficiency. *Ex vivo* approaches might more realistically be considered, but would benefit from progress in the isolation and growth of somatic stem cells and improvements in targeting efficiency." (See abstract). Yanez also teaches that although reports that gene targeting using oligonucleotides have dramatically improved gene targeting frequencies, "Unfortunately, the logarithmic relationship between targeting efficiency and length of homology suggests that simple nucleic acids with small regions of homology will not be sufficient." (See p.153, last paragraph). Regarding the reports that DNA-RNA hybrid oligonucleotides were able to correct a single base mutation of the  $\beta$ -globin gene in immortalized B cells from a patient with sickle cell anemia, Yanez remarks, "as has recently been pointed out, further controls are required to rule out the possibilities of screening artefacts and cell contamination. An unambiguous demonstration of targeted correction would involve the isolation of a clonal cell population bearing both a corrected  $\beta$ -globin allele (as judged by Southern analysis) and an otherwise patient-specific genotype (as judged eg by DNA-fingerprint analysis)." (See p. 154, first paragraph). Yanez states in the final remarks that, "Many old and new questions remain unanswered. We do not understand why different loci appear to target at different frequencies, and whether this may be related to epigenetic factors such as DNA

methylation or chromatin condensation. It is unknown how the proteins of HR [homologous recombination] are recruited to the DSB [double strand break], and little is known about the decision making that drives DSB repair to NHR [non-homologous recombination] and HR" and, "In vivo gene therapy by gene targeting is not viable at present." (See p. 156, under Final Remarks).

More recently, regarding the use of oligonucleotides for targeted gene repair, Gamper et al. (Nucleic Acids Research; Vol. 28, No. 21:4332-4339; 2000) states that the frequency of repair "still represents only a 0.1%-0.2% conversion rate, we may be moving closer to direct applications of gene repair in vivo." (See p. 4338, last paragraph). Indicating that the efficiency of targeted repair still needs improvement. Furthermore, Culver et al. (Nature Biotech. Vol. 17:989-993; 1999) indicates that, "Further experiments with bifunctional oligonucleotides are needed to optimize their structural design, fully characterize the limits on size of mutations that can be repaired, and determine the influences of the various components of the DNA repair complex on the efficiency of correction." (See p. 992, third paragraph).

The claims are also drawn to targeting of nucleic acids in human embryonic stem cells, a method that encompasses stem cell therapy. Regarding stem cell therapy, Kaji et al. (JAMA, Vol. 285, No. 5:545-550; 2001) teaches, "Much additional work remains to be done in the areas of vector development and stem cell biology before the full therapeutic potential of these approaches can be realized. Of equal importance, the ethical issues surrounding gene- and cell-based therapies must be confronted." (See abstract, p. 545).

Working Examples and Guidance in the Specification

The specification has only one working example of using oligonucleotides for successful targeted alteration. The example disclosed is of successful alteration of an episomal nucleic acid in yeast (Example 2, p. 32). As mentioned above, the claims encompass altering any type of genetic material in any prokaryotic cell, or any eukaryotic cell, including yeast, plants, and animals. There are no examples of successful targeting of any type of nucleic acid (such as RNA or chromosomal DNA) in yeast. There are no working examples of successful gene targeting in prokaryotes, or plants or animals (including humans). There are a number of possible genetic disorders that are mentioned as candidates for gene targeting (see Examples 3-25), and the possibility of genetically altering plants using oligonucleotides is also mentioned (see Example 26); however, these examples (Examples 3-26) are only prophetic, and do not disclose the successful alteration of genetic material.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of targeted alteration of genetic material in the large genus of species and of the types of alterations encompassed by the claims would require experimentation testing base addition, deletion and alteration in prokaryotic as well as plant and animal cells, including human cells. Furthermore, experimentation is required to determine the efficacy of gene alteration *in vivo* in plants and animals. Successful *in vivo* application in animals is required before *in vivo* clinical trials in humans can be performed. That is, prior to any therapeutic intervention, it would be necessary to successfully alter genetic material in animal models, in such a way that the genetic alteration treated a disease/disorder, an inventive, unpredictable and difficult undertaking in itself. After experimentation in the animal model(s), the efficacy of the treatment would have to

be tested in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy (including therapeutic gene targeting) recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 25-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25 and 77 are drawn to a method of targeted sequence alteration of a nucleic acid comprising: combining the targeted nucleic acid in the presence of cellular proteins with a single stranded oligonucleotide 17-121 nucleotides in length, said oligonucleotide having an internally unduplicated domain of at least 8 contiguous deoxyribonucleotides. (Emphasis added).

First, the phrase, “in the presence of cellular proteins” renders the claims indefinite because it is unclear if the cellular proteins are in a cell, or are in cell extracts. Therefore, it is unclear if the method is an *in vitro* method or an *in vivo* method.

Second, the phrase “an internally unduplexed domain” renders the claims indefinite because it is unclear how the single stranded oligonucleotide comprises an internally unduplexed domain. There is no definition of the term “unduplexed” anywhere in the specification. Therefore, without a clear definition of “unduplexed” the claims are unclear. For instance, without a clear definition it is unclear if the unduplexed domain is not duplexed with any part of the oligonucleotide, or if the domain does not form a duplex structure with the target nucleic acid.

Additionally, claim 25 recites the limitation "said oligonucleotide DNA domain" in line 11. There is insufficient antecedent basis for this limitation in the claim as there is no prior reference in the claim to any "oligonucleotide DNA domain".

Claim 75 also recites the limitation "said oligonucleotide DNA domain" in line 11. There is insufficient antecedent basis for this limitation in the claim as there is no prior reference in the claim to any "oligonucleotide DNA domain".

Claims 26-74, 76 and 77 are dependent claims and are rejected for the same reasons.

7. Claim 33 recites the limitation "chromosome" in line 2. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 52 recites the limitation "mammal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

9. Claims 57 and 58 recite the limitation "said oligonucleotide DNA domain of claim 25" in line 1. There is insufficient antecedent basis for this limitation in the claim, because the "said oligonucleotide DNA domain" mentioned in claim 25 lacked antecedent basis.

10. Claims 60-62 recite the limitation "said oligonucleotide DNA domain" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, because claim 59 does not specifically recite "oligonucleotide DNA domain".

11. Claims 64-66 recite the limitation "said oligonucleotide DNA domain" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, because claim 63 does not specifically recite "oligonucleotide DNA domain".

12. Claim 69 recites the limitation "said oligonucleotide DNA domain" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, because claim 67 does not specifically recite "oligonucleotide DNA domain".

#### *Claim Rejections - 35 USC § 102*

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 25-29, 35, 36, 53-58, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Sayers et al. (Nucleic Acids Research Vol. 16, No. 3:791-802; 1988).

As mentioned above the claims encompass in vitro as well as in vivo methods of targeted gene alteration.

Sayers teaches an in vitro method of gene alteration using a single stranded oligonucleotide designed to introduce single or double base mismatches, an insertion or a deletion (each of 16 bases) in M13 phage DNA (see abstract). Specifically, Sayers teaches that the targeting oligonucleotide is between 17-121 nucleotides in length (here, 24 nucleotides—see p. 792 last line; and 38 nucleotides, see p. 793, first line). The targeting oligonucleotide of Sayers is a single stranded oligonucleotide that is unduplexed (see p. 792, last paragraph; and p. 793, first paragraph). The oligonucleotides are complementary to the target sequence except for the alterations with the mutations located at least 8 nucleotides from the 5' and 3' termini (see, e.g. figure 1; and p. 792-793). Sayers also teaches that the oligonucleotide has at least one terminal modification, here Sayers teaches that the oligonucleotide is comprised of phosphorothioate linkages (see, e.g. abstract), which constitutes at least three terminal phophorothioate linkages. The targeting reaction of Sayers is in the presence of DNA polymerase I (a cellular protein) (See p. 794, under Repolymerization).

Sayers also teaches that the oligonucleotides targets the (-) strand of the phage (see p. 791, under Introduction), thus the oligonucleotide targets the untranscribed strand of the target nucleic acid.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell  
May 20, 2002

*J*  
JEFFREY FREDMAN  
PRIMARY EXAMINER